

Office Action, p. 13, lines 17-22. Applicants respectfully traverse the rejection with respect to all claims for at least the following reasons: (1) the Examiner has misunderstood and misapplied the holding of In re Wood; (2) without the support of In re Wood, the Examiner has failed to establish a prima facie case of obviousness by failing to cite particular, factual evidence regarding motivation to combine the cited references; and (3) the Braestrup reference teaches away from the instantly claimed invention. Each of these will be discussed in turn below.

The Examiner has misunderstood and misapplied the holding in In re Wood

The lynchpin of the rejection of the present claims under 35 U.S.C. § 103(a) is the use of In re Wood to link the Braestrup and Ho references together. In particular, the Examiner has asserted that In re Wood stands for the proposition that "it is generally well-established that the substitution of methyl-for-hydrogen on a known compound, generally, is not a patentable modification absent unexpected or unobvious results . . ." (citing In re Wood). Office Action, p. 13, lines 17-19. Based on this assertion, the Examiner then searched the literature for a single reference in which the indolic nitrogen atom in the beta-carboline core structure had been substituted with an alkyl group, in this case a methyl group. The search turned up the Ho reference in which beta-carboline compounds were prepared as inhibitors of the monoamine oxidase enzyme. One beta-carboline compound in the Ho reference was substituted at the indolic nitrogen with a methyl group and showed some inhibitory activity. Based on this teaching, and despite the fact that the Examiner recognized that the compound(s) in Ho do not contain the hydroxamic acid moiety of the presently claimed compounds and were prepared in order to inhibit a completely different enzyme, the Examiner asserts that the Braestrup and Ho references are a proper combination to render the presently claimed compounds obvious under 35 U.S.C. § 103(a). Applicants respectfully contend that the Examiner has misunderstood and misapplied the holding in In re Wood and, therefore, because the use of this case is the foundation of the present rejection, the present rejection is error and should be withdrawn with respect to all claims.

In In re Wood, the court affirmed the Board's obviousness rejection of applicants' claims to certain compounds based on a single prior art reference. The claimed compounds were of a certain structural class and were reported to function as antimicrobials. The claimed compounds differed from those found in the prior art reference in that they contained two alkyl groups, such as methyl and ethyl groups, at a particular carbon atom. Additionally, and critical to the court's holding in the case, the prior art reference also taught that the disclosed compounds possessed antimicrobial activity. The court upheld the obviousness rejection based on: (1) the structural similarity between the claimed compounds and those found in the cited reference; and (2) the compound found in the reference was found to have antimicrobial activity. Applicants respectfully contend that the Examiner has misunderstood the holding of the case in making the assertion

that any substitution of "methyl-for-hydrogen" on any compound is unpatentable absent unobvious results. Instead, there is no such per se rule and a fair reading of this case teaches that two tests must be satisfied in order to arrive at a conclusion that one compound is obvious in view of another: (1) "close structural similarity;" and 2) the cited reference must disclose that the compound used as the basis of a rejection has the same utility as those that are claimed. Such an interpretation of the holding of In re Wood is supported by an entire line of later cases from the CCPA and/or the Federal Circuit. This line of cases is discussed below.

First, in In re Payne the court affirmed the Board's rejection of applicants' claims to certain compounds under 35 U.S.C. § 103(a) in view of 5 prior art references. The claimed compounds were disclosed as being useful as pesticides. Importantly, all of the cited prior art references disclosed that the compounds contained therein were also useful as pesticides. The Board's rejection of the claimed compounds relied on two factors, namely the "close structural similarity to, and a community of properties with, the principal reference compounds." In re Payne, 606 F.2d 303, 306, 203 USPQ 245 (CCPA, 1979). In upholding the Board's rejection, the court made it clear that it was doing so because of the "close structural similarity between the claimed compounds at issue here and the compounds of [the prior art references], and because those prior art compounds possess pesticidal activity . . ." (citing In re Wood) Id. at 314. In other words, the court itself read In re Wood as requiring a two-prong test to reach a conclusion of obviousness: (1) close structural similarity; and (2) a teaching that the prior art compounds have the same utility as the claimed compounds.

The court furthered this line of reasoning in In re Lalu, 747 F.2d 703, 223 USPQ 1257 (Fed. Cir. 1984). In this case, the court reversed the Board's rejection of the applicants' claimed compounds as obvious based on compounds found in a prior art reference. The claimed compounds were disclosed as being useful as corrosion inhibiting agents, surface active agents, and leveling agents. The prior art reference relied on by the Board taught compounds that were "homologous" to the claimed compounds and were useful as intermediates for the preparation of other compounds. The Board found that "the close structural similarity between the reference sulfonyl chloride compounds and the claimed compounds was sufficient to raise the presumption of obviousness." Id. at 704. The court reversed the Board's holding and stated that in reaching a conclusion of obviousness, there must always be present in the prior art a practical suggestion that would motivate one of ordinary skill in the art to make the necessary modifications to arrive at the claimed compounds. In this case, there was not sufficient motivation present since the prior art did not teach that the disclosed compounds had the same utility as those that were claimed. Further, the court held that a finding that a prior art compound is useful for any purpose is not sufficient to support a conclusion of obviousness "because we always look to 'the subject matter

as a whole' in determining whether the subject matter 'would have been obvious at the time the invention was made.' Further, a relevant property of a compound cannot be ignored in the determination of obviousness." *Id.* at 706-707 (quoting *In re Papesch*, 50 C.C.P.A. 1084, 315 F.2d 381, 391, 137 USPQ 43, 51 (1963)).

Next, in *In re Grabiak* the court again reversed the Board's finding that applicants' claimed compounds were obvious in view of structurally similar compounds found in the art. In this case, applicants' claimed compounds were disclosed as being useful as herbicidal safeners. The prior art taught compounds that were also herbicidal safeners and differed from the claimed compounds only in that the claimed compounds were thioesters and the prior art compounds were esters (i.e., a sulfur in place of an oxygen). The Board rejected the claimed compounds as obvious based on the assertion that "oxygen and sulfur are well known to be interchangeable," and the "close analogy between sulfur and oxygen isologs is well known." *Id.* at 731. In reversing the Board's finding of obviousness, the court stated that "generalization should be avoided insofar as specific chemical structures are alleged to be *prima facie* obvious one from the other." *Id.* at 731. Furthermore, "[t]he mere fact that is *possible* to find two isolated disclosures which might be combined in such a way to produce a new compound does not necessarily render such production obvious unless the art also contains something to suggest the desirability of the proposed combination." *Id.* at 732 (emphasis in original) (quoting *In re Bergel*, 48 CCPA 1102, 292 F.2d 995, 956-7, 130 USPQ 206, 208 (CCPA 1961)). The court reversed the Board's finding of obviousness because they found nothing in the prior art reference to suggest the making of thioesters from the prior art ester compounds.

Finally, in *In re Jones*, the court reversed the Board's holding that applicants' claims to a particular dicamba salt were obvious in view of prior art references disclosing structurally similar compounds. 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, the Board affirmed the Examiner's rejection of applicants' claimed salt in view of several art prior references and based on the correct, two-prong test enunciated by the court in its prior decisions: (1) a closely related structure; and (2) the common utility of the claimed and prior art compounds. *Id.* at 349. However, the court found in this case that the claimed compound and those in the prior art were not so closely related in structure as to render the former obvious in view of the latter. Importantly, the court made this finding even though the claimed salt was found in the genus described in the prior art. In doing so, they rejected a proposed rule that "regardless of how broad, a disclosure of a chemical genus renders obvious any species that happens to fall within it." *Id.* at 350.

Applicants respectfully contend that the holding and reasoning found in each of these cases clearly establishes that the Examiner erred in stating that *In re Wood* establishes a per se

rule that substitution of methyl-for-hydrogen on a known compound, generally, is not a patentable modification absent unexpected or unobvious results. Rather, each of these decisions clearly teaches that each case must be decided on its own facts and the test for obviousness is two-pronged: (1) a finding of "close structural similarity;" and (2) a finding that the prior art compounds have a common utility to those that are claimed.

In this case, the Examiner has failed to make the requisite findings. In fact, the Examiner admits that the present rejection fails to meet the second prong of the test for obviousness because the compounds found in Braestrup are not reported to share a common utility with those that are presently claimed. In this respect, the Examiner states that "[a]nother difference is that the beta-carboline derivatives in the present invention are used for inhibition of the enzyme 'HIV-integrase,' while the beta-carbolines of the prior art were used as pharmaceuticals 'acting on the central nervous system' (Braestrup) and as 'inhibitors of the enzyme monoamine oxidase' (Ho)". Office Action, p. 14, lines 7-10. The Examiner tries to minimize this fact by stating that "[h]owever, this claims [sic] at issue do not disclose an intended use, but rather just compounds and compositions of Formula (I), so this difference does not affect the analysis." Id., p. 14, lines 10-12. But, it is clear from the cases discussed above that, in reaching a conclusion of obviousness, a finding that the prior art and claimed compounds have a common utility goes to the heart of a finding of motivation to make the claimed compounds. And finding motivation is a necessary component of a conclusion of obviousness (see In re Lee). Therefore, it is clearly legal error for the Examiner to fail to take into account the fact that the prior art does not teach that the disclosed compounds and those that are claimed have a common utility. Such legal error renders the present rejection untenable and Applicants respectfully ask that it be withdrawn.

The Examiner has failed to establish a prima facie case of obviousness

Applicants respectfully submit that they have clearly demonstrated that it is legal error for the Examiner to rely on In re Wood to establish a per se rule regarding the obviousness of a methyl-for-hydrogen modification to a known compound. Absent Examiner's reliance on this per se rule, there clearly is no motivation in either the Braestrup or Ho references to support a conclusion of obviousness with respect to the present claims. In order to establish a prima facie case of obviousness, the Examiner is required to show that the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which such subject matter pertains. 35 U.S.C. § 103(a) (2000). Further, the Court of Appeals for the Federal Circuit has repeatedly held that in order for a prima facie case of obviousness to exist, there must be "some objective teaching in the prior art or . . . knowledge generally available to one of ordinary skill in the art [that] would lead that individual to combine the relevant teachings

of the references." In re Fine, 837 F.2d 1071, 1074 (Fed. Cir. 1988). Last, in finding that particular claims are obvious in view of one or more references, it is the burden of the Office to show that its conclusion to combine such references is based on objective and specific evidence. In re Lee, 277 F.3d 1338 (Fed. Cir. 2002).

In this case, the Examiner has failed to establish a *prima facie* case of obviousness because the rejection contains no objective and specific evidence indicating why one of ordinary skill in the art would have combined the teachings of Braestrup and Ho to arrive at the instantly claimed compounds. In fact, the Examiner has admitted that the Braestrup reference is defective in that: (1) it provides "no specific embodiments of his invention where the substituent on the indolic nitrogen atom . . . was 'C<sub>1</sub>-C<sub>8</sub> alkyl . . .'", Office Action, p. 12, lines 19-20; (2) the "preferred examples and his claims have only 'hydrogen' [on the indolic nitrogen] . . .", Office Action, p. 13, lines 1-2; and (3) the compounds in Braestrup act on the central nervous system, unlike the instant compounds that are inhibitors of the HIV integrase enzyme, Office Action, p. 14, lines 7-10. Applicants also submit that the Braestrup reference is defective for another important reason: it provides no biological data regarding the specific compound identified by the Examiner, wherein R<sup>11</sup> is H, R<sup>12</sup> is -OH, and R<sup>9</sup> is H. Office Action, p. 12, lines 11-14. In fact, this compound is the only compound in the entire Braestrup reference that contains the hydroxamic acid functional group required by the compounds of the present claims. Because there is absolutely no evidence in Braestrup that this particular compound demonstrated any biological activity, Applicants respectfully submit that one of ordinary skill in the art would not have been motivated to modify it in order to arrive at the instantly claimed compounds.

Furthermore, the Examiner has admitted that the Ho reference is defective in that: (1) "the substituted beta-carboline compounds taught in Ho are different than those in the present invention in that the prior art does not disclose a hydroxamic acid substituent at the 3-position of the beta-carboline ring," Office Action, p. 14, lines 4-6; and (2) the compounds in the Ho reference are "inhibitors of the enzyme monoamine oxidase," Office Action, p. 14, lines 9-10. Applicants respectfully submit that one of ordinary skill in the art would not *a priori* expect that a compound useful as an inhibitor of one enzyme is going to necessarily function as an inhibitor of all enzymes, and the HIV integrase enzyme in particular. As such, the Ho reference provides nothing in the way of motivation.

For all of these reasons, the Examiner has failed to cite a specific teaching in either reference that would have motivated one of ordinary skill in the art to modify the compounds found in Braestrup to arrive at those that are presently claimed. As discussed above, the only motivation the Examiner can find to combine the Braestrup and Ho references is the misconception that In re Wood stands for the general proposition that changing a hydrogen atom

for a methyl group on a nitrogen atom is never a patentable distinction, absent unexpected results. Not only is such a reading of Wood legal error, but the court has also stated that the Office cannot remedy deficiencies in cited references by using "general conclusions about what is 'basic knowledge' or 'common sense.'" In re Lee, 277 F.3d 1344. Therefore, Applicants respectfully submit that the Examiner has failed to establish a *prima facie* case of obviousness by failing to demonstrate that either of the cited references contains specific teachings that would have motivated one of skill in the art to modify the disclosed compounds to arrive at the claimed invention. As such, Applicants respectfully request that the rejection be withdrawn with respect to all claims.

The Braestrup Reference Teaches Away from the Claimed Invention

It is well-established that it is impermissible to combine references that teach away from their combination. M.P.E.P. § 2145(X)(D)(2). In this case, the Braestrup reference clearly teaches away from modifying the beta-carboline compounds contained therein as suggested by the Examiner by replacing the hydrogen atom at the R<sup>9</sup> position with any group, particularly carbon-based groups. Applicants wish to direct the Examiner's attention to the compounds found in Table V, columns 12 to 14, of the Braestrup reference. In particular, the 16<sup>th</sup> compound in Table V, wherein R<sup>3</sup> is -NH(C<sub>2</sub>H<sub>5</sub>) and R<sup>9</sup> is -COOC<sub>2</sub>H<sub>5</sub> is the only compound in the entire Braestrup reference that contains anything other than a hydrogen atom on the indolic nitrogen atom. A comparison of the *in vivo* inhibition of flunitrazepam binding of this compound to the fourth compound in Table V, wherein R<sup>3</sup> is -NH(C<sub>2</sub>H<sub>5</sub>) and R<sup>9</sup> is H, shows that compound 16 is much less active, having an ED<sub>50</sub> of > 100 mg/kg s.c., whereas compound 4 demonstrates an ED<sub>50</sub> of 42 mg/kg s.c. In fact, an ED<sub>50</sub> of >100 mg/kg s.c. would likely indicate to one of ordinary skill in the art that compound 16 was inactive *in vivo* at the highest concentration tested. Therefore, one of ordinary skill in the art reading Braestrup would have been dissuaded from preparing compounds containing anything other than a hydrogen atom at the R<sup>9</sup> position. As such, the Braestrup reference teaches away from its combination with the Ho reference with respect to modifications at the indolic nitrogen atom. For this reason alone, Applicants respectfully contend that the present rejection is untenable and ask that it be withdrawn with respect to all claims.

Discussion of other References

Applicants note with thanks the Examiner's conclusion that UK Patent Application No. 2 209 032 A is not germane to the patentability of the present claims.

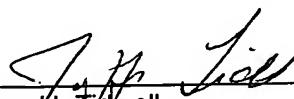
Objections

Claims 5 to 12 are objected to as being dependent upon a rejected base claim. Applicants wish to thank the Examiner for indicating that the subject matter of claims 5 to 12 is allowable. As Applicants believe they have overcome the rejection of claims 1 to 4, the objection to claims 5 to 12 has been rendered moot and Applicants respectfully ask that it be withdrawn.

Last, Applicants hereby petition for any required extension of time. Please charge all required fees to Deposit Account No. 500329.

Respectfully submitted,

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